# Influenza Vaccine Effectiveness Against Hospitalisation and Death in People with Type 2 Diabetes: a retrospective cohort study

Eszter P Vamos, MD, PhD[1], Utz J Pape, PhD[1], Vasa Curcin, MSc, PhD[1], Matthew J Harris, DPhil, FFPH[1], Jonathan Valabhji, MD, FRCP[2], Azeem Majeed, MD, FRCGP[1], Christopher Millett, PhD, FFPH[1]

[1] Department of Primary Care & Public Health, Imperial College London, London, UK

[2] Department of Diabetes and Endocrinology, St Mary's Hospital, Imperial College Healthcare NHS Trust

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**Address for Correspondence:**

Eszter P Vamos MD, PhD

Department of Primary Care and Public Health

Imperial College London,

London W6 8RP

UK

Tel: 00 44 (0) 207 594 7451

Fax: 00 44 (0) 207 594 0854

Email: e.vamos@imperial.ac.uk

Abstract

**Background:** To examine the effectiveness of influenza vaccination against hospitalisation for acute cardiovascular and respiratory conditions and all-cause mortality in people with Type 2 diabetes, while adjusting for residual confounding.

**Methods:** In this retrospective cohort study we used primary and secondary care data from the Clinical Practice Research Database, over 7 years between 2003-2004 and 2009-2010. 124,503 adults with Type 2 diabetes were enrolled. Outcome measures included hospitalisation for acute myocardial infarction (AMI), stroke, heart failure and pneumonia/influenza and mortality. We fitted Poisson regression models for influenza and off-season periods to estimate Incidence Rate Ratios (IRR) for vaccinated and unvaccinated cohorts. Estimates for the summer, when influenza activity is low, were used to adjust for residual confounding.

**Results:** Study participants contributed to 623,591 person-years of observation during the seven cohort years. Vaccine recipients were older and had more co-morbid conditions compared with non-recipients. After adjustment for covariates and residual confounding, vaccination was associated with significantly lower hospitalisation rates for stroke (IRR 0.70 95% CI (0.53-0.91)), heart failure (IRR 0.78 95% CI (0.65-0.92)) and pneumonia or influenza (IRR 0.85 95% CI (0.74-0.99)) and all-cause mortality (IRR 0.76 95% CI (0.65-0.83)), and a non-significant change for AMI (IRR 0.81 95% CI (0.62-1.04) during the influenza seasons.

**Interpretation:** This study demonstrated for the first time that influenza vaccination was associated with reductions in hospitalisation rates for specific cardiovascular events in people

with Type 2 diabetes. Efforts should be focused on improvements in vaccine uptake in this important target group as part of comprehensive secondary prevention.

## Introduction

The health burden caused by seasonal influenza in the general population is substantial and explains much of the excess winter mortality.[1-3] Evidence shows that influenza infection may accelerate acute thrombotic vascular events particularly in patients with ischaemic heart disease and cerebrovascular disease.[4] For decades, vaccination has been the principle strategy to control influenza and its severe complications in the elderly and chronically ill, who account for majority of influenza-attributable deaths.[1] Current influenza vaccination programmes in developed countries were largely implemented based on studies conducted on healthy adults in the 1960s which suggested 70% to 90% vaccine efficacy.[5] In European countries, vaccination is generally restricted groups to the elderly and those with chronic conditions in all adult age groups, and people in close contact with them to reduce transmission.[6] In North America, annual influenza vaccination is universally recommended for all individuals aged 6 months and older.[7, 8]

There has been an on-going controversy about the magnitude of influenza vaccine protection in clinical risk groups and the elderly despite being target populations within many national immunisation schedules.[9] This controversy has been fed by a number of concerns. First, more recent and methodologically sounder studies have reported considerably lower vaccine efficacy in healthy people than earlier studies.[9] Secondly, evidence from placebo-controlled randomised clinical trials demonstrate the effectiveness of influenza vaccine against infection in younger and healthy elderly people, but there is no compelling clinical trial evidence to indicate similar benefits in elderly chronically ill persons.[10] In people with diabetes, an especially high-risk group for influenza-related complications, concerns were raised about impaired immune response to influenza vaccine.[11] Given that national guidelines now strongly recommend influenza vaccination for the elderly and the chronically ill in many

countries, it is anticipated that a placebo-controlled clinical trials conducted among patients with high cardiovascular risk may not receive ethical approval.[9] A few small clinical trials have tested whether influenza vaccine might reduce cardiovascular risk in patients with pre-existing cardiovascular disease.[12] However, to date none of these have been adequately powered to assess impacts on mortality and specific cardiovascular outcomes.[12] Thirdly, methodological studies highlight potential flaws in observational studies, including inadequate adjustment for systematic differences between vaccine recipients and non-recipients (referred to as 'residual confounding').[9, 13]

In people with diabetes, studies assessing influenza vaccine effectiveness are scarce and have shown inconclusive results.[11] None of the previous studies adjusted for residual confounding and most of them reported composite end-points such as hospitalisation for any cause. Furthermore, we are not aware of any studies assessing the potential benefits of influenza vaccination against individual cardiovascular events in people with Type 2 diabetes.[14]

The primary aim of this study is to assess the effectiveness of seasonal influenza vaccine against hospital admissions for acute myocardial infarction (AMI), stroke and heart failure in patients with Type 2 diabetes, while assessing and making further adjustments for residual confounding using estimates obtained for the summer, when influenza activity is minimal. We also assessed the association between influenza vaccine and hospital admission for pneumonia or influenza and all-cause mortality.

## Methods

The Clinical Practice Research Datalink (CPRD) was used for this study. CPRD is one of the world's largest computerised medical databases that holds prospective primary care records.[15, 16] Anonymised primary care data for English practices in the CPRD are now available with a linkage to non-primary-care records including Hospital Episode Statistics (HES) data and Office for National Statistics mortality files.[16] The number of practices participating in the data linkage is 300, representing 65% of participating practices and 5% of the general population in England.[16]

### Study population

We obtained an extract of the records of adults with Type 2 diabetes registered with the 300 family practices participating in the data linkage between 2003-2004 and 2009-2010. Patients with Type 2 diabetes were identified using both diagnostic (C10) and management (66A) Read codes for Type 2 diabetes.[17] Participants for the first cohort year from 1 September 2003 to 31 August 2004 included patients with diabetes who were ≥18 years of age on 1 September 2003 and had been continuously registered with participating practices during the preceding 12 months and throughout the cohort year. For each following study year, patients who newly met the eligibility criteria on 1 September were enrolled.

### Study periods

Each cohort year was categorised into four time periods: pre-influenza, influenza season, post-influenza and summer. Date of the onset and end of influenza season was obtained for each year from national surveillance data on weekly GP consultation rates for influenza-like illness (ILI).[18] According to this surveillance system, influenza season starts when weekly GP ILI activity exceeds the threshold of 30 per 100,000 population and ends when activity goes

below this threshold.[19] We further defined influenza season as the time period from the date of onset to 4 weeks after the end of influenza season to capture delayed complications.

Pre-influenza season was defined as the time period from 1 September to the date of onset of the influenza season. Post-influenza season was defined as the period after the influenza season to 30 April. Summer period was defined as 1 May to 31 August for each cohort year. Pre-influenza, influenza, post-influenza and summer periods were combined across all study years between 2003-2004 and 2009-2010.

Study Variables

The study outcomes included hospital admissions for AMI, stroke, pneumonia or influenza and heart failure and all-cause mortality. Hospital admissions were identified from HES as the principal diagnosis on admission using the 10$^{th}$ revision of International Classification of Diseases (ICD-10) codes as follows: AMI: I21–I22; stroke: I60–I64; influenza/pneumonia: J09–J18; heart failure: I50. During each cohort year, patients were followed from 1 September until the occurrence of study outcomes or end of cohort year (31 August).

Baseline data obtained for each cohort year included age, sex, smoking status (classified as current, ex-smoker, non-smoker or missing), body mass index (BMI), laboratory tests (cholesterol and HbA1c), systolic and diastolic blood pressure readings (SBP and DBP) and number of hospital admissions during the preceding 12 months. Baseline co-morbid conditions were defined using diagnostic Read codes included history of myocardial infarction, stroke, heart failure, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cancer and atrial fibrillation. Medications prescribed were identified from prescription records: insulin, oral anti-hyperglycaemic, anti-hypertensive, lipid lowering,

anticoagulant and antiplatelet drugs and immunosuppressants. We assigned a deprivation score to individual patients, using the Index of Multiple Deprivation 2004 based on their practice postcode.[20] All co-variates were re-defined at the beginning of each cohort year.

Vaccination status

Influenza vaccination status was ascertained from primary care records for each year. In 2009-10, there was an outbreak of a pandemic influenza A(H1N1)pdm09 virus.[18] Due to some unspecific codes that do not allow to discriminate between seasonal and pandemic influenza vaccination, we included all influenza vaccination codes for 2009 and 2010. All study participants were classified as 'unvaccinated' from 1 September until they received influenza vaccine for the subject year. Patients were classified as 'effectively vaccinated' 14 days after the date of vaccination to allow for the attainment of protective antibody titres.[21] We also obtained information on history of pneumococcal polysaccharide vaccination and influenza vaccination during the previous year and.

Statistical analysis

Baseline characteristics of vaccinated and unvaccinated study participants were compared using the Chi-square test for categorical variables, Student's *t* test for normally distributed variables, and Mann-Whitney test for skewed continuous variables, as appropriate.

To estimate incidence rate ratio (IRR) with 95% confidence interval (CI) for vaccinated to unvaccinated cohorts, we fitted random effects Poisson regression models for each outcome. We performed three sets of models for each study outcome and each study period separately: unadjusted (vaccination status as the only predictor), models adjusted for study co-variates and models for the influenza period additionally adjusted for residual confounding.

Co-variates in the adjusted models (second set of models) included age, sex, IMD quintile, duration of diabetes, number of comorbid conditions, smoking status, medications (lipid-lowering drugs, anticoagulants or antiplatelet drugs, anti-hypertensive drugs, insulin, oral anti-hyperglycaemic drugs and immunosuppressive drugs), SBP, DBP, BMI, serum HbA1c, serum cholesterol, number of hospital admissions and influenza vaccination during the previous year, history of pneumococcal vaccination and cohort year.

Vaccine status was considered a time-varying exposure and each patient's follow-up time was classified into vaccinated and unvaccinated person-time periods. Follow-up time was included in the models as an offset term. Study participants could contribute to more than one cohort year in this study. To account for potential within-person dependency, we entered patients as random effects into the models.

We performed an additional analysis to obtain unadjusted and adjusted IRRs and 95% confidence intervals excluding cohort year 2008-2009, when an outbreak of the A(H1N1)pdm09 pandemic strain occurred to test whether the exclusion of this year impacted on the results.

Adjustment for residual confounding

Given that influenza activity is minimal during the summer, vaccination should not provide benefits during the off-season.[22, 23] Therefore, vaccinated and unvaccinated patients should have similar risks of outcomes during the summer period after adjustment for measured confounders with an expected incidence rate ratio (IRR) of 1.0 for the summer period. Effect estimates for the summer period were used to adjust for residual confounding occurring during the influenza period using the following formula.[23, 24]

$IRR_{adjusted} = \exp(\beta_{influenza\ season} - \beta_{summer\ period})$

where β is the regression coefficients obtained from Poisson regression models. To calculate 95% CIs for the effect estimates, we resampled 500 times from the distribution of the observed estimates for the influenza and summer periods. After having taken the difference of each of the 500 sampled estimates, the 2.5$^{th}$ and 97.5$^{th}$ percentile of the distribution was taken to obtain 95% CI for the adjusted IRRs.[23, 24]

In all analyses, a two sided $P \leq 0.05$ was considered statistically significant. We performed statistical analyses using Stata version 11.0.

**Results**

The study included 124,503 patients with Type 2 diabetes who contributed to 623,591 person-years of observation during the 7 study years. During the study period, the predominant circulating influenza strains were A(H3N2) in 2003-2004, 2004-2005, 2006-2007 and 2008-2009, B in 2005-2006 and A(H1N1) in 2007-2008 and 2009-2010 (Table 1).[18] The antigenic match between the circulating and vaccine strains was good for all study years except for 2003-2004 due to antigenic drift and 2009-2010 due to the occurrence of a new variant as a result of antigenic shift.[18] Overall seasonal influenza vaccination uptake in the cohort ranged from 63.1% in 2008-2009 to 69.0% in 2006-2007. Across all study years, there were 5,142 hospital admissions for AMI, 4,515 for stroke, 14,154 for pneumonia or influenza and 12,915 for heart failure and 21,070 deaths were recorded.

Table 2 shows the baseline characteristics of vaccine recipients and non-recipients for the 2003-2004 and 2009-2010 cohorts. Vaccine recipients were older and generally more ill, having more co-existing conditions and larger number of medications prescribed but had lower levels of HbA1c and cholesterol compared with non-recipients.

In unadjusted analyses, there was an inconsistent association between vaccination and outcomes during the flu season. Vaccine recipients compared with non-recipients had significantly higher rates of hospitalisation for AMI and heart failure, lower rates for death and rates did not significantly differ for stroke and pneumonia (Table 3). Vaccination was associated with higher event rates during the summer for all outcomes.

In the models adjusted for study covariates, IRRs attenuated for all study outcomes compared with the unadjusted IRRs. Influenza vaccination was associated with significant

reductions in all study end-points during the influenza season (Table 3). Vaccine recipients had 22% lower rates of AMI (IRR (95% CI) 0.78 (0.65-0.93), P<0.01), 18% lower rates of stroke (0.82 (0.66-1.00)), 17% reduction in heart failure rates (0.83 (0.74-0.93), P<0.001) and 25% lower rates for pneumonia/ influenza (0.75 (0.68-0.82), P<0.001). Furthermore, vaccination reduced mortality rates by 50% during influenza season (IRR 95% CI 0.50 (0.45-0.54), P<0.001). Vaccination was also associated with significantly lower event rates during the pre- and post-influenza seasons for all outcomes except for AMI and pneumonia/influenza for the pre-influenza period (Table 3). However, estimates for the summer period showed differences between vaccinated and unvaccinated patients in these models, indicating insufficient adjustment for underlying differences between these groups.

After adjustment for residual confounding, vaccination was associated with 19% reduction in hospitalisation rate for AMI (IRR (95% CI) 0.81 (0.62-1.04)), 30% reduction in stroke (0.70 (0.53-0.91)), 22% reduction in heart failure (0.78 (0.65-0.92)), and 15% for pneumonia/influenza (0.85 (0.74-0.99)) during influenza season in people who received vaccination compared with unvaccinated people with diabetes (Figure 1). Vaccinated patients had 24% lower death rates compared with non-recipients (IRR (95% CI) 0.76 (0.65-0.83)).

Excluding cohort year 2008-2009 from the analysis when the pandemic A(H1N1)pdm09 was circulating did not qualitatively change the unadjusted and adjusted IRRs obtained for the flu and summer periods (Table 4).

**Interpretation**

In this large population-based study, influenza vaccination of people with Type 2 diabetes was associated with reductions in hospitalisation rates for acute cardiovascular and respiratory diseases and in all-cause mortality across seven influenza seasons. Additional adjustment for residual confounding did not qualitatively alter the results of the conventional analyses but attenuated the associations for AMI, pneumonia/influenza and mortality and strengthened for stroke and heart failure. Vaccine recipients had 30% lower hospitalisation rates for stroke, 22% for heart failure and 15% for pneumonia/influenza and had 24% lower death rates compared with unvaccinated individuals. Influenza vaccination was associated with 19% lower rates of hospitalisation for AMI but this association was not statistically significant.

Current policy in most developed countries strongly emphasizes the annual vaccination of elderly people and patients with chronic conditions including diabetes. However, there is no conclusive clinical trial evidence to support the benefits of influenza vaccination in these groups.[25] In people with diabetes, epidemiological studies quantifying influenza vaccine protection against severe outcomes are scarce and largely inconclusive.[11] A recent meta-analysis found that in patients with diabetes aged 18-64 years, influenza vaccine prevented 58% of all-cause hospitalisations and 43% of hospitalisations for influenza or pneumonia but not mortality.[11] In patients over 65 years, the meta-analysis reported a pooled vaccine effectiveness of 38% for all-cause mortality and 23% for all-cause hospitalisation. However, conclusions were limited by the small number of studies identified, lack of experimental studies, low quality of evidence and strong residual confounding in most studies. The authors did not identify any studies assessing influenza vaccine effectiveness against cardiovascular events.

To better account for the systematic differences between vaccinated and unvaccinated patients, we have made additional adjustments for residual confounding using the summer period when minimal vaccine benefit is expected.[13, 23, 24] Some authors have suggested using the pre-influenza season as a control time period. Many previous studies assessing influenza vaccine effectiveness among elderly people described reduced mortality associated with vaccination during the entire year. Often the association was the largest before influenza was circulating. Jackson et al. argued that frail US seniors did not tend to receive influenza vaccine and die unvaccinated during the follow-up time.[13] They conclude that due to this 'frailty bias', pre-influenza periods are the most suitable for identifying residual confounding because the differences in risk between vaccinated and unvaccinated groups gradually decline over time. However, the pattern of vaccine uptake may largely differ in countries with different immunisation strategies. In North America, influenza vaccine is universally recommended for all over the age of six months and high-risk seniors in the US were found less likely to receive flu vaccine. In England, although the national policy is to offer free influenza vaccine to all people with chronic conditions, the uptake is increasing with advancing age and presence of co-morbid conditions.[26]

Many previous studies examined influenza vaccine effectiveness by analysing one single or a few seasons.[27, 28] There are large variations across years in influenza activity, pathogenicity of circulating strains and degree of vaccine-virus antigenic match. In 2003-2004, vaccine-virus antigenic match was low. An incompletely matched vaccine might provide protection against serologically-confirmed influenza, but to a lesser extent than well-matched vaccines.[21, 29] Due to these variations, evaluating vaccine effectiveness in individual seasons may yield widely

ranging results on vaccine benefits. Our study provides valuable information on the long-term average benefits of influenza vaccine in people with Type 2 diabetes.

In 2009, traditional influenza activity was low but there was an outbreak of a pandemic influenza A(H1N1)pdm09 virus.[18] Similarly to previous pandemics, this strain caused mild illness in most infected individuals and severe disease and mortality mostly affected children and young people.[30] Excluding 2008-2009 from the analyses reduced statistical power due to the reduction in the number of events but did not change the associations found between vaccine and clinical outcomes.

Strengths and limitations

The strengths of this study include the use of a large population-based cohort of patients with Type 2 diabetes, long follow-up time the availability of key laboratory, clinical parameters, and medications as well as the exact date of vaccination. This study assessed for the first time vaccine protection against individual cardiovascular end-points instead of composite outcomes in people with diabetes. Furthermore, we aimed to improve on previous studies by assessing and making further adjustments for residual confounding.

Limitations of this study include that we could not evaluate misclassification of outcomes or co-variates due to undiagnosed cases of outcomes or co-morbidity and unrecorded medical information. However, the validity of CPRD has been continuously monitored and evaluated as high for completeness and accuracy and the database has been extensively used for health research.[15] Furthermore, the study included cohort years during and after the introduction of the Quality and Outcomes Framework when ascertainment and recording of diabetes, co-morbidities and vaccination status are likely to be more accurate due to the financial incentive

provided for general practitioners to record all cases.[31] Uptake of influenza vaccine identified in this study is broadly consistent with published national data.[26] Despite efforts to reduce the effect of selection bias between vaccine recipients and non-recipients, adjustments undertaken using the summer estimates are unlikely to eliminate residual confounding in our observational study.

Concerns about the benefits of influenza vaccination in the elderly and chronically ill largely impacts on the acceptance and uptake of influenza vaccination in many countries including those with comprehensive immunisation programmes.[25] This study has demonstrated that people with Type 2 diabetes may largely benefit from current vaccines including protection against hospital admission against some major cardiovascular outcomes. These findings underline the importance of influenza vaccination as part of comprehensive secondary prevention in this high-risk population.

Declaration of interests: None.

Data sharing statement: Data are available from the CPRD for additional analyses if necessary.

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**Table 1. Characteristics of Study Cohort Years from 2003-2004 to 2009-2010**

| | Study Cohort Year | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2003-2004 | 2004-2005 | 2005-2006 | 2006-2007 | 2007-2008 | 2008-2009 | 2009-2010 |
| Influenza season, week number (date) | | | | | | | |
| Onset | 46 (13 November) | 1 (6 January) | 5 (27 January) | 5 (26 January) | 1 (31 December) | 50 (5 December) | 42 (9 October) |
| End | 49 (5 December) | 6 (11 February) | 8 (23 February) | 9 (1 March) | 2 (13 January) | 3 (15 January) | 49 (3 December) |
| No of patients entering the cohort | 67,067 | 76,215 | 84,780 | 92,732 | 100,187 | 107,323 | 107,013 |
| Total person-years | 66,157.3 | 74,779.1 | 83,111.6 | 90,951.3 | 98,488.5 | 105,218.2 | 104,884.6 |
| No of hospital admissions for | | | | | | | |
| AMI | 639 | 676 | 713 | 725 | 798 | 816 | 775 |
| Stroke | 518 | 561 | 635 | 654 | 702 | 749 | 696 |
| Pneumonia/Influenza | 1,233 | 1,560 | 1,761 | 2,021 | 2,267 | 2,626 | 2,686 |
| Heart Failure | 1,312 | 1,503 | 1,713 | 1,783 | 2,045 | 2,224 | 2,335 |
| No of deaths for all-cause | 1,899 | 2,507 | 2,903 | 3,124 | 3,390 | 3,611 | 3,636 |
| Vaccination coverage, % | 66.54 | 68.4 | 69.0 | 65.7 | 63.9 | 63.1 | 65.0 |
| Vaccine coverage among vaccine recipients by the start of the influenza season, % | 86.1 | 97.7 | 98.9 | 98.5 | 97.3 | 94.0 | 37.8 |
| Predominant virus circulating | A(H3N2) Fujian/411/2002 | A(H3N2) Wellington/01/ 2004 | B Hong Kong/ 330/2001 | A(H3N2) Wisconsin/67/05 | A(H1N1) Solomon Island /3/2006 | A(H3N2) Brisbane/10/2007 | A(H1N1) California/07/2009 |
| Vaccine-virus antigenic match | Low | Good | Good | Good | Good | Good | No match |

*Note:* AMI: Acute Myocardial Infarction

**Table 2.Characteristics of people with diabetes at the baseline of the 2003/04 and 2009/10 cohort years who received and who did not receive influenza vaccination.**

| | 2003-2004 | | | 2009-2010 | | |
|---|---|---|---|---|---|---|
| | Influenza Vaccine | | | Influenza Vaccine | | |
| | Yes | No | P | Yes | No | P |
| No. of subjects (%) | 44,604 (66.5) | 22,463 (33.5) | - | 69,594 (65.0) | 37,419 (35.0) | - |
| Age, yr, mean ± SD | 66.2 ± 13.3 | 56.2 ± 16.3 | <0.001† | 65.8 ± 13.8 | 58.4 ± 17.2 | <0.001† |
| <65 years, N (%) | 17,309 (38.8) | 15,517 (69.1) | <0.001‡ | 29,463 (42.3) | 22,875 (61.1) | <0.001‡ |
| 65-70 years | 8,676 (19.5) | 2,319 (10.3) | | 11,470 (16.5) | 4,491 (12.0) | |
| 71-80 years | 14,006 (31.4) | 3,229 (14.4) | | 20,612 (29.6) | 6,581 (17.6) | |
| 81 years or above | 4,613 (10.3) | 1,398 (6.2) | | 8,049 (11.6) | 3,472 (9.3) | |
| Male sex, N (%) | 24,038 (53.9) | 12,179 (54.2) | | 38,190 (54.9) | 18,971 (50.7) | |
| Smoking, N (%) | | | <0.001‡ | | | <0.001‡ |
| Current | 5,454 (12.2) | 4,442 (19.8) | <0.001‡ | 8,455 (12.2) | 7,087 (18.9) | <0.001‡ |
| Non | 20,774 (46.6) | 10,074 (44.8) | | 33,533 (48.2) | 17,679 (47.2) | |
| Ex | 16,915 (37.9) | 5,996 (26.7) | | 27,515 (39.5) | 10,937 (29.2) | |
| Missing data | 1,461 (3.3) | 1,951 (8.7) | | 91 (0.1) | 1,716 (4.6) | |
| BMI, mean ± SD, $kg/m^2$ | 29.5 ± 6.0 | 30.1 ± 6.5 | <0.001† | 30.5 ± 6.4 | 30.5 ± 6.9 | 0.137† |
| Cholesterol, mean ± SD, mmol/l | 4.7 ± 1.0 | 5.0 ± 1.1 | <0.001† | 4.3 ± 1.0 | 4.6 ± 1.1 | <0.001† |
| SBP, mean ± SD, mm Hg | 141.0 ± 15.9 | 138.9 ± 17.9 | <0.001† | 135.5 ± 14.2 | 134.9 ± 16.6 | <0.001† |
| DBP, mean ± SD, mm Hg | 77.9 ± 8.5 | 80.4 ± 9.8 | <0.001† | 75.9 ± 8.6 | 78.2 ± 9.7 | <0.001† |
| HbA1c, mean ± SD, % | 7.5 ± 1.41 | 7.9 ± 1.80 | <0.001† | 7.3 ± 1.4 | 7.7 ± 1.80 | <0.001† |
| No. of co-morbid conditions, median (IQR) | (0 - 2) | (0 - 1) | <0.001¥ | 1 (0 - 2) | (0 - 1) | <0.001¥ |
| Recorded clinical history, N (%) | | | | | | |
| Heart failure | 4,503 (10.1) | 990 (4.4) | <0.001‡ | 4,578 (6.6) | 1,616 (4.3) | <0.001‡ |
| Stroke | 1,857 (4.2) | 1,504 (6.7) | <0.001‡ | 6,525 (9.4) | 2,604 (6.9) | <0.001‡ |

*Continued Table 2.*

| | 2003-2004 | | | 2009-2010 | | |
|---|---|---|---|---|---|---|
| | Influenza Vaccine | | | Influenza Vaccine | | |
| | Yes | No | P | Yes | No | P |
| Myocardial Infarction | 3,731 (8.4) | 1,313 (5.8) | <0.001‡ | 3028 (8.7) | 2121 (5.7) | <0.001‡ |
| COPD | 4,750 (10.6) | 410 (1.8) | <0.001‡ | 4631 (6.6) | 1203 (3.2) | <0.001‡ |
| Asthma | 5,900 (13.2) | 2,377 (10.6) | <0.001‡ | 10,348 (14.9) | 4,738 (12.7) | <0.001‡ |
| Cancer | 2,524 (5.7) | 773 (3.4) | <0.001‡ | 4,844 (7.0) | 1,627 (4.3) | <0.001‡ |
| Atrial fibrillation | 3,280 (7.3) | 785 (3.5) | <0.001‡ | 5,439 (7.8) | 1,730 (4.6) | <0.001‡ |
| Chronic kidney disease | 2,276 (5.1) | 625 (2.8) | <0.001‡ | 19,164 (27.5) | 5,811 (15.5) | <0.001‡ |
| Medications, N (%) | | | | | | |
| Oral anti-hyperglycaemic | 28,007 (62.8) | 10,438 (46.5) | <0.001‡ | 49,302 (70.8) | 25,305 (67.6) | <0.001‡ |
| Insulin | 9,782 (21.9) | 4,589 (20.4) | <0.001‡ | 14,911 (21.4) | 8,555 (22.9) | <0.001‡ |
| Anti-hypertensive | | | | | | |
| ACE or ARB | 24,476 (54.9) | 7,779 (34.6) | <0.001‡ | 49,092 (70.5) | 19,826 (53.0) | <0.001‡ |
| Beta-blocker | 16,215 (36.4) | 5,547 (24.7) | <0.001‡ | 28,999 (71.8) | 11,402 (30.5) | <0.001‡ |
| Other | 27,897 (62.5) | 8,880 (39.5) | <0.001‡ | 46,316 (66.5) | 18, 350 (49.0) | <0.001‡ |
| Lipid lowering | 22,301 (50.0) | 7,083 (31.5) | <0.001‡ | 57,228 (82.2) | 23,406 (62.5) | <0.001‡ |
| Anticoagulants/antiplatelet | 22,315 (50.0) | 6,458 (28.7) | <0.001‡ | 43,354 (62.3) | 16,875 (45.1) | <0.001‡ |
| Immunosuppressant | 687 (1.5) | 224 (1.0) | <0.001‡ | 1,517 (2.2) | 499 (1.3) | <0.001‡ |
| No of medications, median (IQR) | 4 (2 - 6) | 2 (1 - 4) | <0.001§ | 5 (3 - 7) | 4 (2 - 6) | <0.001§ |
| Hospital admissions during past 12 months, N (%) | 11,552 (25.8) | 4,726 (21.0) | <0.001‡ | 19,531 (28.1) | 9,579 (25.6) | <0.001‡ |
| Pneumococcus vaccine during past 5 years, N (%) | 15,995 (35.9) | 2,638 (11.7) | <0.001‡ | 28,904 (41.5) | 7,627 (20.4) | <0.001‡ |
| Influenza vaccine during past 12 months, N (%) | 35,940 (80.6) | 3,473 (15.5) | <0.001‡ | 60,016 (86.2) | 7,110 (19.0) | <0.001‡ |

*Note*: BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; COPD: Chronic Obstructive Pulmonary Disease; IQR: Interquartile Range; ACE: Angiotensin Converting Enzyme inhibitors, ARB: Angiotensin Receptor Blockers

† Student's t-test; ‡Chi-square test; § Mann-Whitney test

**Table 3. Risk of hospitalisation among people with Type 2 diabetes who received influenza vaccination relative to people who did not receive vaccination for periods before, during and after influenza season and during the summer, across all study years between 2003-2004 and 2009-2010.**

| | | Vaccinated | | | Unvaccinated | | | Unadjusted model[c] | Adjusted model[d] |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | Study Periods[a] | No of events | PY | Rate[b] | No of events | PY | Rate[b] | IRR[e] (95% CI) | IRR[e] (95% CI) |
| Hospital admissions for acute myocardial infarction | Pre-influenza | 452 | 49,181.9 | 9.19 | 1,174 | 135,674.6 | 8.65 | 1.06 (0.95 - 1.18) | 0.91 (0.81-1.03) |
| | Influenza | 580 | 64,633.9 | 8.97 | 329 | 43,597.7 | 7.55 | 1.18 (1.03 - 1.36)* | 0.78 (0.65 - 0.93)** |
| | Post-influenza | 712 | 80,677.7 | 8.83 | 316 | 43,305.6 | 7.30 | 1.20 (1.05 - 1.38)** | 0.87 (0.71 - 1.05) |
| | Summer | 1,133 | 139,014.5 | 8.15 | 446 | 72,567.9 | 6.15 | 1.32 (1.18 - 1.47)*** | 0.96 (0.82- 1.12) |
| Hospital admissions for stroke | Pre-influenza | 323 | 49,210.8 | 6.56 | 1,102 | 135,678.7 | 8.12 | 0.81 (0.71 - 0.91)*** | 0.74 (0.65 - 0.85)*** |
| | Influenza | 486 | 64,688.4 | 7.51 | 310 | 43,594.4 | 7.11 | 1.05 (0.91 - 1.21) | 0.82 (0.67 – 1.00) |
| | Post-influenza | 559 | 80,768.3 | 6.92 | 331 | 43,291.6 | 7.65 | 0.90 (0.78 - 1.03) | 0.73 (0.59 - 0.89)** |
| | Summer | 1,046 | 139,220.9 | 7.51 | 358 | 72,555.7 | 4.93 | 1.53 (1.35 - 1.73)*** | 1.17 (1.00-1.41) |
| Hospital admission for heart failure | Pre-influenza | 1,180 | 49,005.6 | 24.08 | 3,199 | 135,431.5 | 23.62 | 0.99 (0.92 - 1.06) | 0.88 (0.82 - 0.95)*** |
| | Influenza | 1,617 | 64,288.5 | 25.15 | 813 | 43,412.2 | 18.73 | 1.28 (1.17 - 1.40)*** | 0.83 (0.74 - 0.93)*** |
| | Post-influenza | 1,790 | 80,067.4 | 22.36 | 676 | 43,008.7 | 15.72 | 1.40 (1.27 - 1.53)*** | 0.84 (0.73 - 0.95)** |
| | Summer | 2,770 | 137,484.2 | 20.15 | 870 | 71,943.3 | 12.09 | 1.65 (1.52 - 1.79)*** | 1.06 (0.95 - 1.18) |
| Hospital admission for pneumonia/influenza | Pre-influenza | 1,245 | 49,076.0 | 25.37 | 3,007 | 135,478.0 | 22.20 | 1.15 (1.07 - 1.23)*** | 1.08 (1.01 - 1.17) |
| | Influenza | 1,908 | 64,331.7 | 29.66 | 1,307 | 43,326.2 | 30.17 | 0.96 (0.89 - 1.03) | 0.75 (0.68 - 0.82)*** |
| | Post-influenza | 1,989 | 80,081.9 | 24.84 | 919 | 42,845.0 | 21.45 | 1.15 (1.06 - 1.25)*** | 0.86 (0.77 - 0.97)** |
| | Summer | 2,623 | 137,505.4 | 19.08 | 1,156 | 71,571.1 | 16.15 | 1.18 (1.10 - 1.27)*** | 0.88 (0.80 - 0.98)* |
| All-cause mortality | Pre-influenza | 1,381 | 49,243.8 | 28.04 | 4,441 | 135,812.9 | 32.70 | 0.86 (0.81 - 0.91)*** | 0.77 (0.72 - 0.83)*** |
| | Influenza | 2,294 | 64,569.0 | 35.53 | 1,797 | 43,029.2 | 41.76 | 0.85 (0.80 - 0.90)*** | 0.50 (0.45 - 0.54)*** |
| | Post-influenza | 2,838 | 80,362.3 | 35.32 | 1,464 | 42,403.0 | 34.53 | 1.02 (0.96 - 1.09) | 0.58 (0.52 - 0.65)*** |
| | Summer | 4,732 | 137,644.4 | 34.38 | 2,123 | 70,526.3 | 30.10 | 1.14 (1.08 - 1.20)*** | 0.66 (0.61 - 0.72)*** |

[a] Pre-influenza season was defined as the time period from 1 September to the onset of the influenza season. Influenza season was defined as the time period from the onset to the end of the influenza season and an additional 4 weeks to capture delayed complications. Post-influenza season was defined as the period after the influenza season to 30 April each year. Summer period was defined as 1 May to 31 August for each cohort year.

[b] Rates are expressed as per 1,000 patient years

[c] Models with vaccination status as the only predictor

[d] Models are adjusted for age, sex, Index of Multiple Deprivation quintile, number of comorbid conditions, duration of diabetes, body mass index, smoking status, systolic and diastolic blood pressure, serum cholesterol and HbA1c, lipid-lowering drugs, anticoagulants or antiplatelet drugs, anti-hypertensive drugs, insulin, oral anti-hyperglycaemic drugs and immunosuppressive drugs, number of hospital admissions during previous year, history of Pneumococcus vaccination, influenza vaccination during previous year and cohort year.
[e] IRR: Incidence Rate Ratio, *** P≤0.001; ** P≤0.01; * P≤0.05

**Table 4. Risk of hospitalisation among people with Type 2 diabetes who received influenza vaccination relative to people who did not receive vaccination for influenza season and summer between 2003-2004 and 2009-2010, excluding 2008-2009 when the outbreak of pandemic A(H1N1)pdm09 occurred.**

| | | Unadjusted model[b] | Adjusted model[c] |
|---|---|---|---|
| Outcome | Study Periods[a] | IRR[d] (95% CI) | IRR[d] (95% CI) |
| Hospital admissions for acute myocardial infarction | Influenza | 1.17 (1.01 - 1.36)* | 0.76 (0.62 - 0.93)** |
| | Summer | 1.27 (1.13 - 1.44)*** | 0.91 (0.77- 1.08) |
| Hospital admissions for stroke | Influenza | 1.07 (0.91 - 1.25) | 0.86 (0.69 – 1.07) |
| | Summer | 1.44 (1.26 - 1.64)*** | 1.13 (0.93-1.36) |
| Hospital admission for heart failure | Influenza | 1.25 (1.14 - 1.38)*** | 0.82 (0.72 - 0.93)** |
| | Summer | 1.59 (1.45 - 1.74)*** | 1.03 (0.91 - 1.16) |
| Hospital admission for pneumonia/influenza | Influenza | 0.97 (0.89 - 1.05) | 0.76 (0.68 - 0.85)*** |
| | Summer | 1.19 (1.09 - 1.28)*** | 0.89 (0.79 - 0.99)* |
| All-cause mortality | Influenza | 0.87 (0.81 - 0.93)*** | 0.52 (0.47 - 0.58)*** |
| | Summer | 1.14 (1.08 - 1.21)*** | 0.67 (0.61 - 0.73)*** |

[a] Influenza season was defined as the time period from the onset to the end of the influenza season and an additional 4 weeks to capture delayed complications. Summer period was defined as 1 May to 31 August for each cohort year (excluding 2008-2009 from the analysis)

[b] Models with vaccination status as the only predictor

[c] Models are adjusted for age, sex, Index of Multiple Deprivation quintile, number of comorbid conditions, duration of diabetes, body mass index, smoking status, systolic and diastolic blood pressure, serum cholesterol and HbA1c, lipid-lowering drugs, anticoagulants or antiplatelet drugs, anti-hypertensive drugs, insulin, oral anti-hyperglycaemic drugs and immunosuppressive drugs, number of hospital admissions during previous year, history of Pneumococcus vaccination, influenza vaccination during previous year and cohort year.

[d] IRR: Incidence Rate Ratio, *** P≤0.001; ** P≤0.01; * P≤0.05